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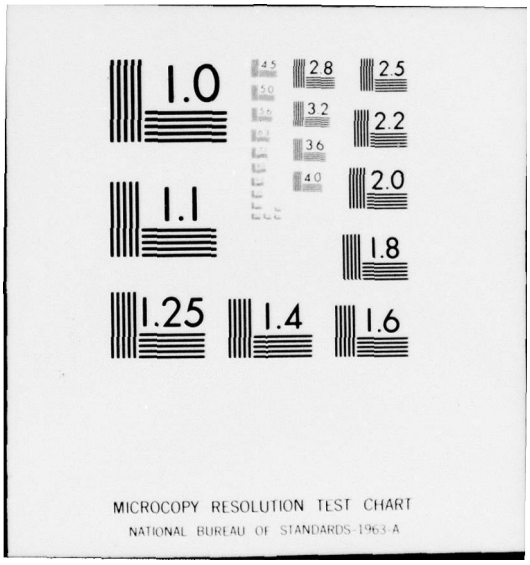
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EDGEWOOD ARSENAL TECHNICAL REPORT
EB-TR-76117

DOSE-RESPONSE EFFECTS OF INTRAVENOUS THIAMINE HYDROCHLORIDE ON PRALIDOXIME PHARMACOKINETICS IN MAN

By

John Josselson, M.D., MAJ, MC, USAR
Frederick R. Sidell, M.D.

Biomedical Laboratory

March 1977

DEPARTMENT OF THE ARMY
Headquarters, Edgewood Arsenal
Aberdeen Proving Ground, Maryland 21010

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Five subjects were given pralidoxime chloride (5 mg/kg, iv) alone or at the end of the first hour of a 3-hour infusion of thiamine hydrochloride (100 mg/hr on one occasion and 200 mg/hr on another). Plasma concentrations of pralidoxime were significantly higher when the oxime was given during a thiamine infusion; plasma concentrations of the oxime were increased slightly more when the higher dose of thiamine was infused. Total oxime excretion was equal in the three groups, but the thiamine-treated groups excreted less oxime during the first 6 hours after drug administration. This suggests that thiamine caused higher concentrations of oxime in the blood by blocking the renal excretion of the drug.

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PREFACE

The work described in this report was authorized under Project/Task 1W762710AD2502, Medical Defense Against Chemical Agents, Prophylaxis and Therapy for Lethal Agents. This work was started in January 1975 and completed in March 1975.

The volunteers in these tests are enlisted US Army personnel. These tests are governed by the principles, policies, and rules for medical volunteers as established in AR 70-25 and the Declaration of Helsinki.

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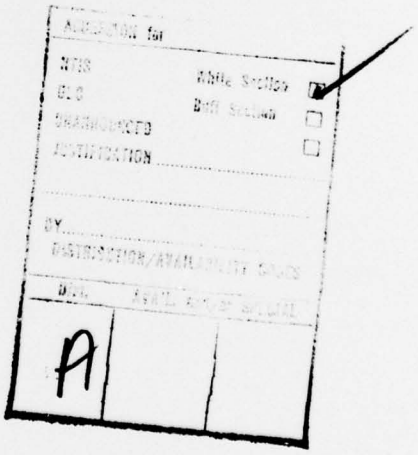

CONTENTS

DOSE-RESPONSE EFFECTS OF INTRAVENOUS THIAMINE HYDROCHLORIDE ON PRALIDOXIME PHARMACOKINETICS IN MAN

I. INTRODUCTION.

The cholinesterase reactivator, pralidoxime chloride (N-methylpyridinium-2-aldoxime), remains the drug of choice in this country for the definitive treatment of organophosphate anticholinesterase poisoning, and is generally used in conjunction with one of the belladonna alkaloids, usually atropine. The major limitations in the use of all of the currently available oximes have been the production of gastrointestinal side effects (nausea and vomiting with the risk of aspiration in an unconscious patient), hypertension when used in large doses (above 20 mg/kg), and the short half-life and rapid excretion of the drugs. Previous studies in this laboratory have shown that thiamine hydrochloride, U.S.P., when administered either intravenously or intramuscularly immediately before or concomitant with the administration of a rapid intravenous injection of pralidoxime, will significantly increase the plasma half-life and plasma oxime concentration and delay the excretion of the oxime, presumably without altering the mode of excretion.*,[1] The study presented here was directed toward determining whether or not the response to thiamine was a dose-related event. Thus, subjects were tested according to previous protocols but, on this occasion, using two different doses of thiamine HCl.

II. METHODS.

A. Subjects.

The subjects were US Army enlisted personnel who agreed to the protocol after thorough explanation and discussion. Screening included complete physical and laboratory examinations [chest X-ray, ECG, complete blood count, routine urinalysis, blood urea nitrogen, serum creatinine, liver function tests (SGOT, alkaline phosphatase, serum bilirubin)]. A detailed history of allergy was obtained and intradermal scratch testing with thiamine was performed to exclude potentially hypersensitive subjects.

B. Design.

Five subjects participated and received two different doses of thiamine, each serving as his own control. Subjects entered the ward on the evening before the study, ate a light breakfast about 1 hour before the study began, and drank about 1 to 2 liters of fluid in the 2 hours that preceded drug administration.

C. Controls.

At the start of testing, a continuous infusion of normal saline into the anticubital vein was begun and continued for 3 hours (200 ml/hr). One hour after the infusion was started, each subject received an intravenous injection of pralidoxime chloride (2-formyl-1-methylpyridinium chloride oxime),** 5 mg/kg, for 2 minutes through the scalp needle of the infusion line.

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* Josselson, J., and Sidell, F. R. EB-TR-76115. The Effect of Thiamine Hydrochloride on Pralidoxime Pharmacokinetics in Man. Submitted for publication.

** Protopam, Ayerst Laboratories, New York, New York. 10017.

D. Thiamine Treatment (100 mg/hr).

At the start of testing, a continuous infusion containing normal saline and thiamine hydrochloride* was begun; the thiamine was delivered at a rate of 100 mg/hr over a 3-hour period (0.5 mg thiamine/ml of normal saline, 200 ml/hr). One hour after the infusion was begun, each subject received an injection of pralidoxime, 5 mg/kg, as in the control test.

E. Thiamine Treatment (200 mg/hr).

This trial was conducted in the same manner except that the thiamine was delivered at a rate of 200 mg/hr over a 3-hour period (1.0 mg thiamine/ml of normal saline, 200 ml/hr).

The study was randomized and each administration was performed 1 week apart, so that on any given day pralidoxime chloride alone and with both doses of thiamine was administered.

Timed urine collections were obtained from all subjects at 1.5, 3.0, 6.0, and 24 hours. Plasma specimens were obtained through an indwelling scalp needle in a vein in the opposite arm, kept open with heparin, at 0.05, 0.10, 0.15, 0.25, 0.50, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, and 6.0 hours after the injection of oxime. Plasma and urine were analyzed by the method of Groff, *et al.*[2] for oxime. Subjective responses to both thiamine and pralidoxime were monitored. Subjects were kept in bed during the 3-hour infusion period, thereafter, they were allowed to walk about.

F. Calculations.

The serial plasma oxime concentration, when plotted against time, fit the curve described by the bi-exponential equation 1 which describes the disposition of drug in a two-compartment

$$Cp = Ae^{-\alpha t} + Be^{-\beta t} \qquad (1)$$

model. In this equation, Cp is the plasma concentration, t is the time, A and B represent the zero time intercepts of the linear components of the rapid and slow portions of the plasma decay curve, and α and β represent the slopes of these two lines divided by -2.303. A more detailed description of the derivations of this equation is provided by Wagner[3] and devised with respect to pralidoxime in studies by Swartz *et al.*[4] and Sidell.[5] The computer program NONLIN[6] was used to estimate the parameters of the equation. From these the following were calculated:

1. The half-life of the rapid equilibrium phase ($t_{1/2}\,\alpha$) and the slower elimination phase ($t_{1/2}\,\beta$)

2. The volumes of distribution of the central compartment (V_1), the peripheral compartment (V_2), and the total volume (V_D)

3. The rate constants for drug movement from central to peripheral compartment (K_{12}), from peripheral to central compartment (K_{21}), and for elimination from the central compartment (K_{13})

4. The plasma and renal clearance of pralidoxime. The plasma clearance was

*Thiamine Hydrochloride Injection U.S.P., 10 mg/ml, Natcon Chemical Co.

calculated by dividing the dose of pralidoxime by the area under the plasma concentration versus time curve (which was obtained from the integral of equation 1), and the renal clearance was obtained by dividing the amount of pralidoxime excreted into the urine during a given time period by the area under the curve for that time interval.

III. RESULTS.

A. Clinical Findings.

Both thiamine and pralidoxime were well tolerated by all subjects with no major untoward side effects. No changes in vital signs were observed during the course of all three trials. All five subjects, during the control testing, complained of subjective visual disturbances, ranging from "blurring" to "heavy eyelids;" one complained of actual diplopia. These symptoms occurred only transiently in controls (lasting up to 10 minutes), were present in four of the five subjects during treatment with the low dose of thiamine (100 mg/hr), lasting up to 1 hour, and were present in all subjects receiving 200 mg/hr of thiamine, persisting up to 2 hours in four of the five subjects. Three subjects complained of prolonged lethargy and drowsiness following the high dose of thiamine, but these symptoms disappeared by the morning after testing.

B. Plasma Concentration.

The mean plasma concentrations of pralidoxime are plotted in the following figure. After 3 minutes (0.05 hr), statistically significant differences were noted when controls were compared with both the low-dose (T_1) thiamine group ($p < 0.05$, paired t test) and the high-dose (T_2) thiamine group ($p < 0.05$, paired t test), and when the T_1 group was compared to the T_2 group ($p < 0.05$, paired t test) up to hour 5 of plasma collection.

C. Urinary Excretion of Pralidoxime (Table 1).

Over the 24-hour period of urine collection, there was no significant difference in total oxime excretion among the three groups. The controls (C) excreted 74.8% (±12 SD); the low dose thiamine group (T_1) 66.7% (±6.7 SD); and the high-dose thiamine group (T_2) 69.1% (±7.6 SD) of their doses of pralidoxime. However, over the first 6 hours, the thiamine-treated groups eliminated significantly less oxime [C 71% (±11 SD); T_1 49.9% (±8.7 SD); T_2 43.6% (±67 SD)] when compared to controls ($p < 0.01$, paired t test), but not when compared to each other. Additionally, over the last 18 hours (6 to 24 hours) of timed urine collection, significantly more oxime appeared in the urine of both thiamine-treated groups when compared to controls and to each other [C 3.4% (±3 SD); T_1 16.8% (±5.3 SD); T_2 25.5% (±7 SD) (C vs T_1 $p < 0.01$; C vs T_2 $p < 0.01$; T_1 vs T_2 $p < 0.05$; paired t test)].

D. Renal Clearance.

Mean renal clearance data are presented in table 1. The 24-hour renal clearance of oxime was reduced significantly in both thiamine-treated groups, when compared to controls and to each other (C vs T_1, $p < 0.05$; C vs T_2, $p < 0.05$; T_1 vs T_2, $p < 0.05$, paired t test).

Table 1. Urinary Recovery of Pralidoxime

Time	C	T_1	T_2	p[a]
hr				
A. Mean Cumulative Excretion of Pralidoxime Over 24 Hours[b]				
0-1.5	77.4±[c] 5.5	45.3± 5.8	34.6± 3.5	0.01 0.001 0.05
0-3	0.5± 4.8	54.6± 7.0	48.9± 6.1	0.001 0.001 NS
0-6	95.1± 4.9	74.5± 8.9	63.4± 8.4	0.01 0.01 0.05
0-24	100	100	100	-
B. Mean Urinary Excretion of Pralidoxime for Each Collection Period[b]				
0-1.5	77.4± 5.5	43.5± 5.8	34.6± 3.5	0.01 0.001 0.05
0-5.3	13.1± 3.3	11.1± 1.9	14.3± 2.7	NS NS NS
3-6	5.0± 3.6	19.8± 3.4	14.5± 4.6	0.001 0.02 NS
6-24	4.5± 4.3	25.5± 8.9	36.8± 8.7	0.01 0.01 0.05
Total	100	100	100	-

[a] C versus T_1.
C versus T_2.
T_1 versus T_2.
[b] Expressed as percent of the total amount of oxime excreted in the urine.
[c] Mean ± SD.
NOTE: NS – not sufficient.

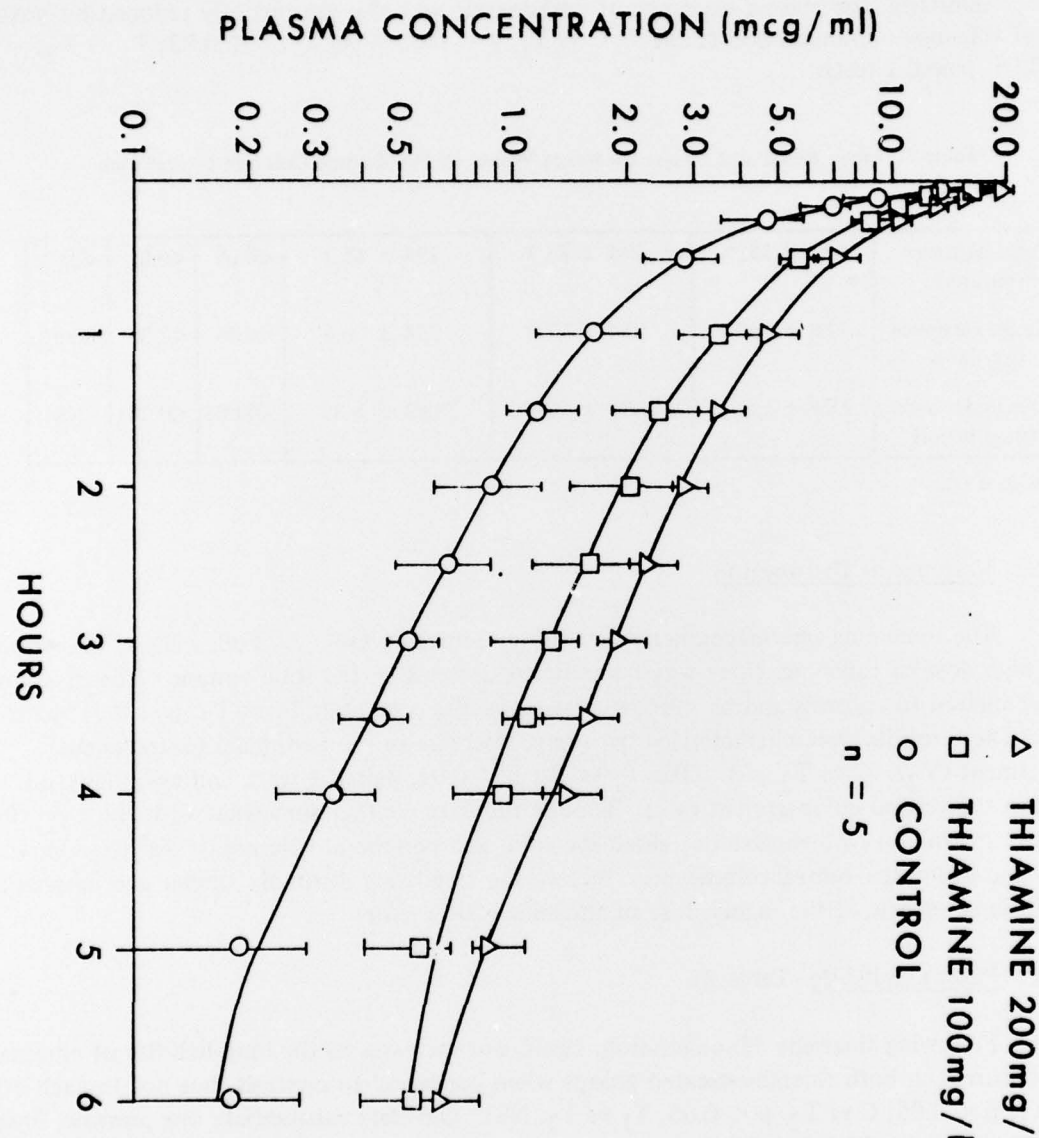

Figure. A Plot of the Mean Concentrations of Pralidoxime

IV. KINETIC DATA.

A. Plasma Clearance.

Similarly, the plasma clearance of pralidoxime was also significantly reduced by both levels of thiamine administration (table 2: C vs T_1, $p < 0.05$; C vs T_2, $p < 0.02$; T_1 vs T_2, $p < 0.05$, paired t test).

Table 2. Mean Renal and Plasma Clearance Values of Pralidoxime Chloride in Five Men

Renal clearance (ml/min)	603 ± 352*	245 ± 83.7	178 ± 55.1	<0.05	<0.05	<0.05
Plasma clearance (ml/min)	774 ± 308	364 ± 97.8	258 ± 76.5	<0.05	<0.02	<0.05
Area under curve (mcg. hr/ml)	7.04 ± 1.85	14.36 ± 2.86	20.93 ± 6.89	<0.001	<0.001	NS

*Mean ± SD.

B. Volumes of Distribution.

The remaining pharmacokinetic data are presented in table 3. Following administration of the high dose of thiamine, there was a significant decrease in the total volume of distribution when compared to controls and to the low dose (C vs T_2, $p < 0.02$; T_1 vs T_2, $p < 0.01$, paired t test). These results were characterized by a large decrease in the peripheral (extravascular) compartment (V_2), (C vs T_2, $p < 0.02$; T_1 vs T_2, $p < 0.02$, paired t test), and essentially no change in the central compartment (V_1). Though the data conflict somewhat with those previously reported* in which low dose also decreased the total and peripheral volumes of distribution while slightly increasing the central volume, nevertheless, the trends are distinctly similar and emphasize the additional effects of the higher dose of thiamine (200 mg/hr).

C. Plasma Half-Life (Table 2).

Following thiamine administration, significant increases in the long half-life of elimination ($t_{1/2\beta}$) occurred in both thiamine-treated groups when compared to controls, but not to each other (C vs T_1, $p < 0.05$; C vs T_2, $p < 0.05$; T_1 vs T_2, NS). Our data substantiate our previous findings* that thiamine hydrochloride (100 mg/hr) did prolong the short (or equilibration phase) half-time ($t_{1/2\alpha}$), but data comparing the control dose with the high dose of thiamine and comparing the high and low doses of thiamine showed no significance.

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Table 3. Pharmacokinetic Parameters

	Control	Thiamine 1	Thiamine 2	Statistical significance (p)		
				C vs T_1	C vs T_2	T_1 vs T_2
"Short" Half-Time ($t_{1/2}$) (hr)	0.07 ± 0.005*	0.14 ± 0.03	0.14 ± 0.11	<0.01	NS	NS
"Long" Half-Time ($t_{1/2}$) (hr)	0.99 ± 0.13	1.46 ± 0.24	1.52 ± 0.47	<0.05	<0.05	NS
k_{21} (hr^{-1})	2.37 ± 0.44	1.94 ± 0.43	2.64 ± 1.40	NS	NS	NS
k_{13} (hr^{-1})	2.94 ± 0.75	1.32 ± 0.26	1.21 ± 0.47	<0.01	<0.01	NS
k_{12} (hr^{-1})	4.95 ± 0.40	2.49 ± 0.78	3.21 ± 1.85	<0.001	NS	NS
V_1 (central) (ml/kg)	259 ± 40.7	275 ± 39.5	232 ± 71.4	NS	NS	NS
V_2 (peripheral) (ml/kg)	563 ± 178	335 ± 29.5	257 ± 101	NS	<0.02	<0.02
V_D (total) (ml/kg)	822 ± 211	618 ± 48.8	469 ± 49.1	NS	<0.02	<0.01

*Mean ± SD.

D. Equilibrium Constants (Table 3).

Following the low dose of thiamine, a highly significant decrease occurred in the rate constant (K_{12}) governing movement of oxime from the central to the peripheral compartments (C vs T_1, $p < 0.001$, paired t test), but no trends were identified when the high dose of thiamine was compared to the low dose or controls (C vs T_2, p: NS; T_1 vs T_2, p: NS, paired t test)

Significant changes also occurred in the rate constant (K_{13}) when controls were compared to both thiamine levels (C vs T_1, $p < 0.01$; C vs T_2, $p < 0.01$, paired t test), but no significant differences were noted between the two thiamine-treated groups. The changes noted reflected the decrease in renal (and plasma) clearance before and after pretreatment with thiamine.

V. DISCUSSION.

That the half-life, renal and plasma clearances, and pharmacokinetics can be altered by prior or simultaneous administration of thiamine hydrochloride intramuscularly or intravenously has been demonstrated conclusively by this and previous studies.*,[1] The data presented here are in close agreement with our previous report, and the minor differences [especially with respect to half-life ($t_{1/2\beta}$), volumes of distribution, and rate constants] appear to be due to the limited size of our population (n=5). Nevertheless, the experience in this laboratory over the past 2 years with a total of 20 subjects substantiates our findings.*,[1]

*Josselson, J., and Sidell, F. R. EB-TR-76115. The Effects of Thiamine Hydrochloride on Pralidoxime Pharmacokinetics in Man. Submitted for publication.

Likewise, the fact that the higher dose of thiamine hydrochloride (200 mg/hr) should be more effective than the lower dose (100 mg/hr) was also not unexpected. Though the higher dose did not significantly alter the long plasma half-life ($t_{1/2\beta}$), it did increase it slightly. More importantly, however, the higher dose did significantly decrease both renal and plasma clearance of oxime when compared to the lower dose and, perhaps even more importantly, did maintain significantly higher plasma levels of oxime over the first 4 hours of treatment.

Though pralidoxime is well recognized as an effective cholinesterase reactivator in the treatment of organophosphate nerve agent and insecticide poisoning, few, if any, objective criteria have been established to indicate what parameters one can monitor to achieve successful therapy. Clearly, the patient must be treated rapidly (within at least 2 hours). Available information on antidotes suggests that the optimal plasma concentration for effective regeneration of the inhibited enzyme is approximately 4 mg%. If this is the case, then the intravenous administration of the high dose of thiamine (200 mg/hr infusion) appears to be advantageous over low-dose therapy (100 mg/hr) and will maintain levels of 4 mg% for up to 1 hour. Low-dose therapy holds that level for only 30 minutes, and when there is no pretreatment, the plasma concentration falls below the 4 mcg/ml level in 15 minutes (at oxime doses of 5 mg/hr). At this point, oxime re-administration may be necessary.

While the higher dose of thiamine did markedly prolong the clinical side effects of oxime and did produce more lethargy than the low-dose therapy, it was, in general, excellently tolerated by all subjects. Use of this procedure may avoid the problems involved with larger doses of oxime (i.e., hypertension and gastrointestinal disturbances).

Studies are now under way to determine whether drip infusion of pralidoxime and thiamine hydrochloride over 1 to 2 hours will be statistically effective. Once studies have been performed in an adequately simulated casualty situation, better determination of the effectiveness of thiamine hydrochloride should be possible.

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